Electromicroscopic Investigation of the Efficacy of FactorXIII for Coil Embolization in Experimental Aneurysms

Preliminary Report

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Summary

In recent years, endovascular treatment has often been used to treat cerebral aneurysms. Basic investigation to elucidate the process of endothelial cell growth within aneurysms is a crucial problem. We performed elecrtro-detachable coil embolization in aneurysms under administration of blood coagulation factor XIII, a wound-healing accelerator, and examined changes in endothelial cells on the surface of the inserted coil with a scanning electron microscope.

Experimental aneurysms produced in animals were treated by coil embolization and histological changes in embolized coil after the treatment of factorXIII were investigated.

Aneurysms were produced in four matured swines under general anesthesia and coil embolization was performed with a elecrtro-detachable coil. The aneurysms were resected immediately and 3 weeks after coil embolization, and investigated histologically with a scanning electron microscope. Seven animals were administrated with blood coagulation factor XIII on the day of embolized and the following 4 consecutive days. These aneurysms were also resected 3 weeks after embolization and investigated histologically.

More marked fibroblast proliferation and growth of endothelial cells on the surface of luminal side of embolized coil were seen in the aneurysms in the group administrated with factor XIII than in aneurysms treated without factor XIII.

More effective and sufficient coil embolization can be obtained by administration of factor XIII.

Introduction

In recent years, electro-detachable coil (EDC), which can be safely detach using electricity, has been used frequently [1-3]. To become an alternative therapy to clipping, however, several problems still have to be overcome for this technique. The problems include the displacement and migration of a coil, incomplete embolization of the aneurysm, and coil compaction and cerebral infarction [3]. The level of thrombosis within the aneurysm and growth of endothelial cells after coil embolization, which influence the patients' long-term prognoses, have not yet been evaluated definitively [1,2,3,7]. Basic investigation to elucidate the process of endothelial cell growth within aneurysms is a crucial problem.

We performed EDC embolization in experimental aneurysms using factor XIII, a wound-healing accelerator, and examined changes in endothelial cells on the surface of the inserted coil with a scanning electron microscope.

Methods

All animals experiments were conducted accordance with policies set by the Kyorin university school of medicine Animal Research Committee and National Institutes of Health guidelines. Four matured swines (weighing 25-30 kg) were premedicated with ketamine (20 mg/kg, i.m.) and atropine sulfate (0.02 mg/kg, i.m.), and incubated after premedication with 5% halothane to introduce general anesthesia with 2-4% halothane and 1 L of oxygen. Intravenous infusion of heparin-added physiological saline and respiration monitoring, ECG monitoring were conducted for the duration of anesthetizing. A median incision of the neck was made to expose the external carotid artery branching from the common carotid artery. And the region approximately 2 cm distal to the bifurcation of the external carotid artery and the ascending pharyngeal artery were ligated with a 2-0 silk thread to make an experimental aneurysms. A 5 Fr sheaths was placed in right femoral artery selective common carotid angiogram was performed using a 5 Fr catheter. A micro-catheter was inserted through the catheter and placed into the aneurysm. The aneurysm was embolized with EDC (2 mm x 8 cm, 3 mm x 8 cm) under the fluoroscope.

A these procedures treated aneurysms produced by the above method were resected immediately and 3 weeks after. Aneurysms were also resected in the same way from animals which were administreted with blood coagulation factor XIII (Fibrogammin P: Aventis Phara Ltd., Tokyo, Japan), 3 units daily for 5 consecutive days beginning immediately after the embolization of the aneurysms and resected 3 weeks after the treatment. After the aneurysms were removed, all animals were sacrificed by an injection of a fatal dose of ketamine. The embolized aneurysms were fixed and histologically examined on the surface of coil focusing upon the change in endothelial cells and fibroblasts with a scanning electron microscope.

Results

The aneurysms removed immediately after embolization without factor XIII showed blood constituents remaining on the surface of the coil, but no growth of fibroblasts or endothelial cells. However, aneurysms resected 3 weeks after embolization showed apparent growth of fibroblast cells with incomplete covering of the coil surface by endothelial cells.

On the other hand, the aneurysms administrated with factor XIII resected 3 weeks after embolization showed multi-layered fibroblasts overlying the coil and endothelial cells with continuity with the endothelial cells in the periphery in the lumen covering the surface of the coil. Marked growth of fibroblasts, and endothelial cells were obvious in the aneurysms administrated with factor XIII as compared with the aneurysms that had received without factor XIII.

Discussion

In recent years, endovascular coil embolization has being become common treatment for intracerebral aneurysms. Guglielmi have developed a coil whose action can be terminated by electricity. A minimal electric current sent to an aneurysm accelerates the thrombosis within the aneurysm, because a positively charged platinum coil draws negatively charged blood cells and fibrinogen. EDC is increasingly being used because of its simplicity of handling [1,2,3]. However, its efficacy on thrombosis, proliferation of fibroblasts, and growth of vascular endothelial cells has not yet been definitively assessed [4-7]. Guglielmi reported that the mortality and morbidity of 42 cases, treated EDC embolization are 4.8%(two cases) and 2.4%(one cases), respectively [3]. Although coil embolization is considered to be useful in high-risk cases and anatomically difficult cases, the evaluation of recanalization, regrowth, and rupture are required in the long-term follow-up [3,20]. On the other hand, Factor XIII bridges the fibrin molecules that is major effects on the proliferation of fibroblasts and rearranges the fibrin network, and thereby accelerates the proliferation of fibroblasts. Factor XIII promotes collagen synthesis in a wound and thereby plays an important role in its healing [10].

Endovascular intervention in aneurysms has become safer in accordance with the modification of catheters, and development of the coil. However, in attaining safe embolization it is very important to understand thrombosis, the proliferation of fibroblasts, and the growth of endothelial cells occurring in an embolized aneurysm. Reported results from basic and

clinical studies vary from ones which state that the surface of the lumen of the aneurysm was covered with endothelial cells [5-7,21], to those which state that endothelial growth was not sufficient [4,19]. Therefore, there is no established common view with respect to changes in the endoluminal surface of aneurysms after the treatment. Furthermore, the level and duration of thrombosis after embolization are incompletely understood. Kang et Al reported that treatment by hemostasis and wound-healing factor XIII produced endothelial growth in the lumen of an experimental aneurysm [11]. Some investigators conducted histological investigation of endoluminal changes in experimentally produced aneurysms after treatment with protein-coated EDC or a collagen-coated microcoil.

In the substrate of factor XIII used as a coating material, markedly increased proliferation of fibroblasts was observed, and thus thrombosis could be increased [12-18]. In the present study, we used factor XIII, a wound-healing factor, in embolization, and identified marked proliferation of fibroblasts, and growth of endothelial cells in experimentally produced aneurysms.

Conclusions

Factor XIII accelerated the proliferation of fibroblasts and the growth of endothelial cells. The use of factor XIII after coil embolization is considered to be important to perform safe and efficacious embolization. Further investigation of this technique in a large group and evaluation of blood levels of factor XIII should be performed.

References

1 Guglielmi G, Viñuela F et Al: Electothrombosis of saccular aneurysm via endovascular approach; Part 1. J Neurosurg 75: 1-7, 1991.
2 Guglielmi G, Viñuela F et Al: Electothrombosis of saccular aneurysm via endovascular approach; Part 2. J Neurosurg 75: 8-14, 1991.
3 Guglielmi G, Viñuela F et Al: Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils. J Neurosurg 77: 515-524, 1992.
4 Andrew JM, David WE et Al: Histological findings in giant aneurysms treated with Guglielmi detachable coils. J Neurosurg 83: 129-132, 1995.
5 Tenjin H, Fukui S et Al: Effect of Guglielmi detachable coils on experimental carotid artery in primates. Stroke 26: 2027-2080, 1995.
6 Michel EM, Janine KM et Al: Long-term histopathologic changes in canine aneurysms embolized with Guglielmi detachable coils. Am J Neuroradiol 16: 7-13, 1995.
7 Gerhard B, Volkan T et Al: Gross and microscopic histopathological findings in aneurysms of the human brain treated with Guglielmi detachable coils. J Neurosurg 91: 284-293, 1999.
8 Matsuda M: Blood coagulation Factor XIII, pasteurized. Diagnosis and Treatment 74: 2171-2176, 1986.
9 Hirahara K, Shinbo K et Al: Suppressive effect of human blood coagulation factor XIII on the vascular permeability induced by anti-guinea pig endothelial cell antiserum in guinea pigs. Thomb Res 71: 139-148, 1993.
10 Isogai N, Ueda Y et Al: Wound healing at the site of microvascular anastomosis; fibrin-stabilizing factor XIII administration and its effect. Microsurgery 11: 40-46, 1990.
11 Kang Y, Hashimoto N et Al: Effects of blood coagulation factorXIII on the development of experimental cerebral aneurysms in rats. J Neurosug 73: 242-247, 1990.
12 Robet CD, Ali FK et Al: Treatment of experimental aneurysms using collagen-coated microcoils. Neurosurgery 36: 133-140, 1995.
13 Murayama Y, Viñuela F et Al: Development of biologically active GDC for the treatment of cerebral aneurysms. Interventional Neuroradiology 5: 211-231, 1999.
14 Tamatani S, Ozawa T et Al: Radiologic and histopathologic evaluation of canine artery occlusion after collagen-coated platinum microcoil delivery. Am J Neuroradiol 20: 541-545, 1999.
15 Murayama Y, Viñuela F et Al: Ion implantation and protein coating of detachable coils for endovascular treatment of cerebral aneurysms: concepts and preliminary results in swine models. Neurosurg. 40: 1233-1244, 1997.
16 Tamatani S, Ozawa T et Al: Histological interaction of cultured endothelial cells and endovascular embolic materials coated with extracellular matrix. J Neurosurg 86: 109-112, 1997.
17 Arvin AA, Pobert WH et Al: Platinum coil coatings to increase thrombogenicity: a preliminary study in rabbits. Am J Neuroradiol 14: 794-798, 1993.
18 Istvan S, Ajay KW et Al: Initial experience with collagen-filled Guglielmi detachable coils for endovascular treatment of experimental aneurysms. Am J Neuloradiol 18: 67-672, 1997.
19 Konishi Y, Van VH et Al: Evaluation of acute thrombogenesis following microcoil aneurysm treatment in swine, Advances in Intravascular radiology and Intravascular Neurosurgery, 45-50, 1996.
20 Manabe H, Fujita S et Al: Rerupture of coil-embolized aneurysm during long-term observation. J Neurosurg 88: 1096-1098, 1998.
21 Miyachi S, Negoro M et Al: Histopathological study of balloon embolization; silicone versus latexe. Neurosurg 30: 483-489, 1992.

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